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Self-Rated Health Predicts Mortality and Graft Loss after Kidney Transplantation: A 10-Year Follow-Up Study

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Key Words
Graft loss · Kidney transplantation · Mortality · Self-rated health

Abstract
Background: This study explored whether self-rated health (SRH) shortly after kidney transplantation (KT) predicts mortality and graft loss at up to 10 years' follow-up. ***Methods:*** A total of 276 patients shortly after successful KT were interviewed. SRH was measured using the first item of the SF-36 questionnaire and divided into three tertiles: poor, average and excellent health. Clinical data were retrieved from medical records. Cox regression was used to identify whether different levels of SRH predicted mortality and graft loss in transplant recipients. The observation period was up to 10 years. ***Results:*** Poor SRH (HR 11.1, $p < 0.001$), average SRH (HR 4.21, $p < 0.05$), estimated glomerular filtration rate (HR 0.26, $p < 0.05$) and age (HR 1.04, $p < 0.05$) were significantly associated with mortality. Similarly, poor SRH (HR 6.4, $p < 0.001$), average SRH (HR 3.6, $p < 0.05$), new-onset diabetes mellitus after KT (HR 3.3, $p < 0.05$) and chronic renal allograft dysfunction (HR 3.7, $p < 0.00$) were significantly associated with graft loss. ***Conclusion:*** Poor SRH shortly after transplantation indicates an increased risk of mortality and graft loss at up to 10 years' follow-up. SRH could be an inexpensive and reliable indicator for starting diagnostic and/or treatment strategies. The usefulness of SRH compared to other global clinical measures predicting mortality and graft loss should also be studied.

Introduction

Self-rated health (SRH) is an independent predictor of mortality in patients with end-stage renal disease (ESRD) on chronic dialysis [1]. Persons with poor SRH have a higher mortality risk compared with those with excellent SRH, even after controlling for a range of demographic and clinical variables [1, 2]. Previous studies have also shown that physical, psychological and total scores of health-related quality of life were significantly correlated with increased risks of ESRD and death in patients with chronic kidney disease, independent of comorbidity factors [3, 4].

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The medical predictors of mortality are also known. A study by Desai and co-workers [5] has shown that cardiovascular and inflammatory markers were predictors of mortality and might have important implications for risk stratification in the ESRD population. Other studies have demonstrated the associations between infections, graft rejections, donor and recipient factors with increased mortality and graft loss in kidney transplantation (KT) recipients [6–9]. Ravindran et al. [10] explored the idea that new-onset diabetes mellitus after transplantation was a well-recognized complication of solid organ transplantation associated with higher patient mortality and graft loss.

Many studies in ESRD, including those after transplantation, have shown medical factors to be associated with mortality and graft loss [6–10]. Moreover, Novak et al. [11] showed that depressive symptoms were an independent predictor of mortality-censored graft loss in patients after KT. Surprisingly, we found no studies on SRH as a predictor of mortality or graft loss in KT recipients.

The aim of this prospective observation study is to explore whether SRH in an early period after KT predicts mortality and graft loss at up to 10 years' follow-up.

Methods

Sample and Procedure

A total of 362 consecutive patients who underwent KT between January 2001 and January 2011 at the Transplant Centre of Kosice in the eastern region of Slovakia were enrolled in the study. The baseline examination of the participants occurred between the third and twelfth month after successful KT. The first 3 months after KT are usually considered to be the most problematic period connected to dramatic changes, increased morbidity and even mortality [12]. Furthermore, improvement in self-perceived health most often occurs during the first 2 years after KT [13]. Before the first 3 months after KT, 9 (2.5%) patients were not included because 3 (0.8%) of them had died and 6 (1.7%) had lost their transplanted kidney. The exclusion criteria were the presence of mental retardation, acquired cognitive impairments, severe dementia or other psychiatric diseases mentioned in the medical record. After the exclusion of 1 (0.3%) patient because of the exclusion criteria, a total of 352 KT recipients after successful transplant surgery were invited to participate. Of those, 34 (9.7%) refused to participate, 31 (8.8%) did not return the questionnaire, and 11 (3.1%) provided questionnaire with missing data, resulting in a total of 276 patients (an effective response rate of 78.4%) at the start of the study. Figure 1 presents more detailed information on participants.

Patients provided information about sociodemographic variables and filled in the questionnaire. All participants were interviewed during regular outpatient clinical visits by trained personnel independent of the transplant team. Medical data were retrieved from medical records at the same time as sociodemographic data and data of SRH.

Only patients who signed an informed consent prior to the study were included. The local ethics committee in Kosice approved the study.

Measures

Sociodemographic data included age, gender and education. Age was treated as a continual variable. We categorized education into elementary (primary school, completed or not), apprenticeship (completed, or not-completed secondary school), secondary (completed, or not-completed university) and university (completed).

SRH was measured using the first question of the Short Form Health Survey (SF-36) [14]. The answer options 1 (poor), 2 (fair), 3 (good), 4 (very good) and 5 (excellent) were transformed into a standard scale from 0 (poor health) to 100 (excellent health) in which the higher scores indicate a better health status [14]. This scale was then categorized into tertiles: scores 0–30 (fair and poor) were categorized as 'poor health'; 31–60 (good) as 'average health', and 61–100 (excellent and very good) as 'excellent health' [15]. The validity and reliability of the first item of the SF-36 has been confirmed in patients with renal disease, including those after KT [16–18].

Clinical data were retrieved from medical files. These included serum creatinine, previous duration of dialysis (in years), primary kidney diagnosis, source of transplanted kidney, function immediately after KT, comorbidity, the current and rejection immunosuppressive treatment, acute rejection episodes, chronic renal allograft dysfunction, uroinfection, which included pyelonephritis, comorbidities and diagnosis of graft loss, and mortality. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula [19]. Acute rejection episodes and chronic renal allograft dysfunction were diagnosed from biopsy according to the Banff 2009 update of diagnostic categories for renal allograft biopsies [20].

Statistical Analysis

The Mann-Whitney U test and χ^2 test were used to test the differences between respondents and non-respondents. Frequencies, means and standard deviations were calculated for the sample description. Both tests were used to identify the association between the dependent variables (mortality and graft loss), and the other variables: age, gender, education, SRH categorized into tertiles (excellent SRH – reference category), eGFR at baseline, uroinfection (pyelonephritis included), number of acute rejection episodes, chronic renal allograft dysfunction, source of transplanted kidney, cardiovascular disease – coronary artery disease, cardiac failure, myocardial infarction and categories of diabetes mellitus (no diabetes mellitus – reference category, already existing diabetes mellitus and new-onset diabetes mellitus after transplantation). Cox regression (conditional LR method) was performed in order to identify the predictors of mortality (censored for graft loss) and predictors of graft loss. The independent variables in both Cox regression models were all variables with $p < 0.1$ in Mann-Whitney U test and χ^2 test, as appropriate. Harrell's C-statistic and Somers' D were calculated for both models (model for mortality and model for graft loss). The Statistical Package for the Social Science (SPSS, Inc., Chicago, Ill., USA) version 18.0.3 and STATA/SE 11.1 were used for statistical analyses.

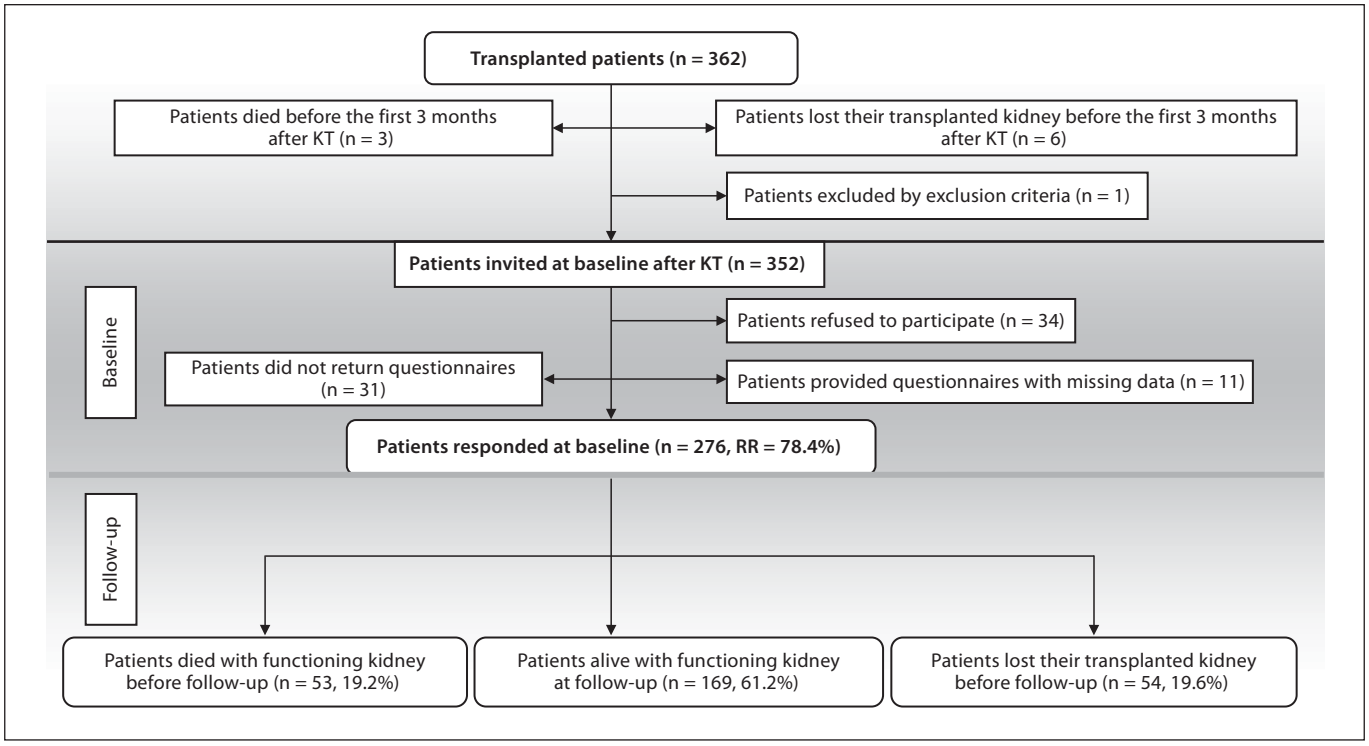

Fig. 1. Flow-chart diagram of the participants. RR = Response rate; n = number; KT = kidney transplantation.

Results

No significant differences were found between respondents and non-respondents regarding age and gender. Also, no significant differences were found between those who provided complete and incomplete data in age, gender, mortality and graft loss. The observation period was up to 10 years (mean 5.8 ± 2.7) of follow-up; the mean period for poor SRH was 4.5 ± 0.2 years, for average SRH 6.5 ± 0.2 years and for excellent SRH 6.6 ± 0.4 years. The mean period between transplantation and mortality for poor SRH was 3.8 ± 1.5 years, for average SRH 6.2 ± 3.5 years and for excellent SRH 7.2 ± 2.6 years. The mean period between transplantation and graft loss for poor SRH was 4.2 ± 2.3 years, for average SRH 5.6 ± 1.5 years and for excellent SRH 7.3 ± 1.7. During the observation period, 40 patients with poor SRH (39.2%) died and 31 (30.4%) lost their transplanted kidney; 11 with average SRH (9.0%) died and 20 (16.4%) lost their graft and 2 with excellent SRH (3.8%) died and 3 (5.8%) lost their graft. Table 1 displays detailed information about the characteristics of the sample (n = 257).

The Mann-Whitney U test showed that age ($p < 0.001$) and eGFR ($p < 0.001$) were associated with mortality. Age ($p < 0.001$), eGFR ($p < 0.001$), and the number of acute rejection episodes ($p < 0.05$) were associated with graft loss. The χ^2 test was performed in order to identify factors associated with mortality and graft loss, and the findings were that SRH ($\chi^2 = 45.2$; $p < 0.001$) and cardiac failure ($\chi^2 = 2.7$; $p = 0.1$) were associated with mortality, while SRH ($\chi^2 = 15.9$; $p < 0.001$), chronic renal allograft dysfunction ($\chi^2 = 42.7$; $p < 0.001$), and diabetes ($\chi^2 = 4.5$; $p < 0.1$) were associated with graft loss. These associations are marked in table 1, and the mentioned variables were used as independent factors in both Cox regression models (model 1 for mortality and model 2 for graft loss).

Acute rejection episodes and cardiac failure were not predictors associated with mortality and graft loss in either Cox regression model. For mortality, Harrell's C-statistic remitted 0.88 and Somers' D 0.75. Poor (HR 11.1, 95% CI 4.22; 29.04, $p < 0.001$) and average (HR 4.21, 95% CI 1.3; 13.71, $p < 0.038$) SRH contributed significantly to this model, as did eGFR (HR 0.98, 95% CI 0.96; 1.0, $p < 0.021$) and age (HR 1.04, 95% CI 1.0; 1.09, $p < 0.03$). Regarding this, the risk of death was increased by 4% for each year of age; on the other hand, the risk of death was decreased by 2% for each 1 ml/min/1.73 m^2 eGFR (ta-

Table 1. Characteristics of the sample (n = 276)

		Number (%) or mean ± SD	Mortality	Graft loss
Age		48.27 ± 12.34	*	**
Gender	male	164 (59.4)		
	female	112 (40.6)		
Education	elementary	48 (17.4)		
	apprenticeship	125 (45.3)		
	secondary	81 (29.3)		
	university	22 (8.0)		
SRH		49.4 ± 1.56	*	**
Category of SRH	poor	102 (37.0)	*	**
	average	122 (44.2)	*	**
	excellent	52 (18.8)	*	**
Duration on dialysis before KT, years		3.66 ± 3.04		
Primary diagnosis of kidney failure	glomerulonephritis	98 (35.5)		
	tubulointerstitial nephritis	65 (23.6)		
	vascular disease	26 (9.4)		
	polycystic kidneys adult type	25 (9.1)		
	diabetic nephropathy	18 (6.5)		
	other/unknown	44 (15.9)		
Source of transplanted kidney	deceased donor	262 (94.9)		
	living donor	14 (5.1)		
Function immediately after KT	immediate	157 (56.88)		
	delayed	119 (43.12)		
Acute rejection episodes		93 (33.7)		**
Type of rejection treatment	steroids	72 (27.9)		
	antithymocyte globulin	10 (3.6)		
	plasmapheresis	6 (2.2)		
	plasmapheresis + i.v. immunoglobulin	5 (1.8)		
Chronic renal allograft dysfunction		42 (15.2)		**
Uroinfection		84 (30.4)		
Immunosuppression treatment at baseline	CsA+P	35 (12.7)		
	CsA+AZA/CsA+AZA+P	24 (8.7)		
	CsA+MMF/CsA+MMF+P	139 (50.4)		
	Tac+MMF/Tac+MMF+P	73 (26.4)		
	SIR+MMF+P/EVER+CsA+MMF	5 (1.8)		
eGFR (ml/min/1.73 m^2) at baseline		58.8 ± 19.8	*	**
Comorbidities	coronary artery disease	78 (28.3)		
	cardiac failure	72 (26.1)	*	
	myocardial infarction	17 (6.2)		
	hypertension	226 (81.9)		
	diabetes mellitus identified before KT	18 (6.5)		
	new-onset diabetes mellitus after transplantation	17 (6.2)		**
	chronic kidney disease-mineral bone disorder	160 (58.0)		
	other comorbidities: ≥2	9 (3.3)		
Diagnosis of graft loss	acute rejection episodes	5 (9.3)		
	chronic renal allograft dysfunction	16 (29.6)		
	uroinfections	14 (25.9)		
	others/unknown	19 (35.2)		
Diagnosis of mortality	acute myocardial infarction	25 (47.2)		
	pulmonary disease/pulmonary embolism	7 (13.2)		
	stroke	3 (5.7)		
	carcinoma/liver disease	6 (11.3)		
	others/unknown	12 (22.6)		

* Association with mortality ($p < 0.1$); ** association with graft loss ($p < 0.1$).

ble 2). Figure 2 displays the differences in mortality between poor, average and excellent SRH. For graft loss, Harrell's C-statistic was 0.84 and Somers' D 0.68. Poor (HR 6.43, 95% CI 2.98; 13.85, $p < 0.001$) and average (HR 3.58, 95% CI 1.26; 10.2, $p < 0.017$) SRH contributed significantly to this model, as did chronic renal allograft dysfunction (HR 3.71, 95% CI 1.82; 7.6, $p < 0.001$) and new-onset diabetes mellitus after transplantation (HR 3.29, 95% CI 1.16; 9.34, $p < 0.015$). In line with this, chronic renal allograft dysfunction was associated with a 3.7-fold higher and new-onset diabetes mellitus after transplantation with a 3.3-fold higher risk of graft loss (table 2). Figure 3 displays the differences in graft loss between poor, average and excellent SRH.

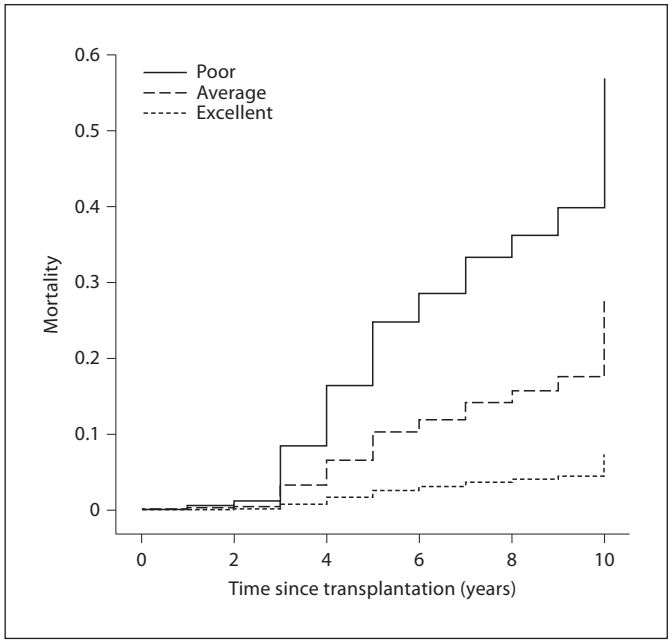

Fig. 2. Differences in mortality between poor, average and excellent SRH over 10 years.

Discussion

In this study we explored SRH in an early period after KT as a predictor of mortality and graft loss in KT recipients at up to 10 years' follow-up. In addition to SRH, age and eGFR were predictors of patient mortality. The predictors for graft loss were SRH, chronic renal allograft dysfunction and new-onset diabetes mellitus after transplantation. In line with our findings, Kutner and coworkers [21] showed that physical functioning might be used together with factors in pretransplant recipients to prove their potential risk for morbidity, graft loss and mortality after KT.

In the Cox regression model for mortality, we found that patients with a higher eGFR had a significantly reduced mortality hazard ratio. On the other hand, average SRH was associated with a 4-fold higher and poor SRH with an 11-fold higher risk of mortality. In the Cox regression model for graft loss, we found that chronic renal allograft dysfunction, new-onset diabetes mellitus after KT and average SRH were associated with a 3-fold higher risk of graft loss, and poor SRH was associated with a 6-fold higher risk of graft loss. Much like our findings of the risk ratio for graft loss, many studies have explored the idea that graft rejection and new-onset diabetes mellitus increased the graft loss risk ratio [9, 22]. Surprisingly, cardiovascular disease was not associated with mortality or graft loss in our sample, which is probably due to underdiagnosis, as we relied on evidence in the medical records and did not actively evaluate patients' comorbidity.

To our knowledge, when searching the literature we found no study exploring whether there is an association of SRH with mortality and graft loss in KT recipients. Tanikella et al. [23] in their study with 3 years' follow-up explored whether liver-transplanted patients with lower self-reported physical quality of life had an increased risk of mortality. So far, studies on dialysis patients have established a significant connection between poorer SRH and higher risk of mortality [1, 3, 4]. Spiegel et al. [24] in their systematic review explored a close connection between poor well-being, morbidity and mortality in patients with ESRD. These findings are in line with our results. Thus, SRH might reflect several adverse conditions and therefore may provide additional information on a patient's risk, independent of demographic, socioeconomic and clinical risk factors for mortality [15] and graft loss.

Strengths and Limitations

The strength of this study is the prospective follow-up for 10 years, which enabled us to explore SRH and the others factors as predictors of mortality and graft loss after KT. Moreover, all consecutive patients originating from one major transplant center in Slovakia over a number of years were asked to participate in the study to prevent selection bias.

Missing data is a limitation of this study; on the other hand, there were no differences in age and gender be-

Table 2. Final models of Cox regression containing significant predictors of mortality (model 1) and graft loss (model 2)

Models	2log likelihood	B(SE)	Hazard ratio	95% CI for hazard ratio
Model 1 – Mortality (n = 276); Harrell's C-statistic = 0.88; Somers' D = 0.75				
Age	365.39	0.04 (0.02)*	1.04	1.00; 1.09
Estimated glomerular filtration rate	356.59	–0.02 (0.01)*	0.98	0.96; 1.00
Self-rated health				
Poor		2.41 (0.49)***	11.1	4.22; 29.04
Average	323.62	1.44 (0.60)*	4.21	1.30; 13.71
Excellent			reference	
Model 2 – Graft loss (n = 276); Harrell's C-statistic = 0.84; Somers' D = 0.68				
Chronic renal allograft dysfunction	398.97	1.31 (0.37)***	3.71	1.82; 7.60
New-onset diabetes mellitus after transplantation	379.86	1.19 (0.53)*	3.29	1.16; 9.34
Self-rated health				
Poor		1.86 (0.39)***	6.43	2.98; 13.85
Average	363.78	1.28 (0.53)*	3.58	1.26; 10.20
Excellent			reference	

B(SE) = Unstandardized coefficient B (standard error). * $p < 0.05$, *** $p < 0.001$.

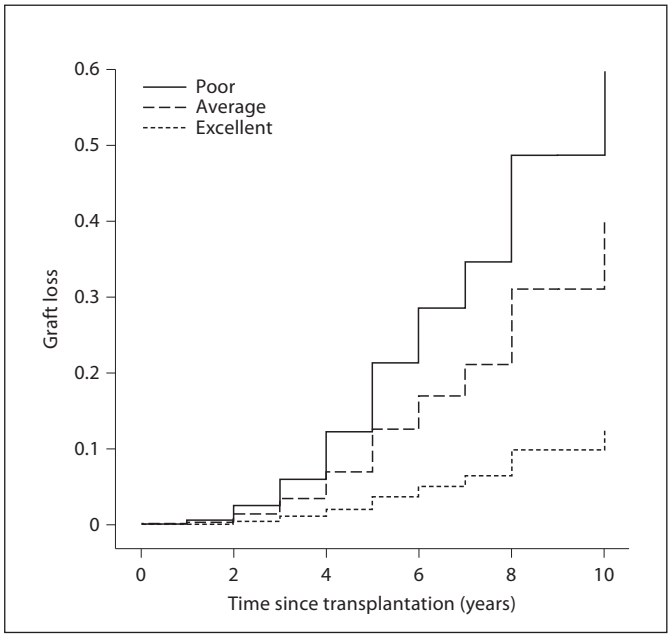

Fig. 3. Differences in graft loss between poor, average and excellent SRH over 10 years.

tween respondents and non-respondents, and no differences in age, gender, mortality and graft loss between recipients who provided complete and incomplete data. The variable observation period between minimum and maximum (1 and 10 years) is also a limitation. The SRH interviews were not conducted immediately after transplantation to prevent false findings due to perioperative stress. Therefore, patients who died or lost their transplanted kidney before the first 3 months after KT were not incorporated into the study. It could be of interest to control for a potential effect of pretransplantation SRH, as it may predict mortality and graft loss as well. Our findings might only be used partially due to their potential lack of generalizability, as we used data from a single-center sample.

Policy Implications

SRH could be used as an inexpensive and swift predictor of risky KT recipients. Patients with poor SRH might undergo relevant clinical as well as laboratory assessment and/or treatment to reduce their high risk of mortality and graft loss.

Recommendations for Further Research

Results must be verified in a larger multicenter sample to allow for generalization. We could then verify whether SRH after KT remains a predictor of mortality and graft loss in KT recipients, or whether in a longer period after KT other variables become important. Furthermore, the pathways between psychological, physical and medical determinants associated with SRH, mortality and graft loss should be studied.

Conclusion

Poor and average SRH in an early period after transplantation indicated a higher risk of mortality and graft loss at up to 10 years' follow-up. Poor SRH is associated with an 11-fold higher risk of mortality and a 6-fold higher risk of graft loss compared to excellent SRH at up to 10 years' follow-up. Patients with poor SRH might undergo relevant clinical as well as laboratory assessment and/or treatment to reduce their high risk of mortality and graft loss.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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